

The effects of age-related changes in color vision on the ability of  
older adults to properly take medication

By: Lindsay K Skomrock

The Ohio State University  
College of Pharmacy  
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Advisor: Virginia E. Richardson  
The Ohio State University  
College of Social Work

### **Abstract**

**Background:** Prescription compliance is a complex issue, affected by physical, psychological, and emotional factors. Changes in color vision due to the normal aging process are an aspect of declining physical functioning that has not been addressed in relation to prescription compliance.

**Objective:** To establish a relationship between medication selection and color vision loss in older adults.

**Methods:** This study with healthy younger adults, age 18-26, used a pair of yellow-lens glasses and colored beads to simulate medication selection in older adults compared with a control group of similarly aged adults not wearing the lenses. Medication selection was quantified by correct bead selection and complexity of challenge was determined by a difficulty rating.

**Results:** Participants with the yellow-lens glasses were only able to select the correct color of bead 74.4% of the time compared to 100% for the control group. The experimental group also expressed more difficulty with the task giving it a difficulty rating of 4.02 out of 5 compared to 1.04 out of 5 in the control group.

**Conclusions:** This study concluded that older persons were more likely to have difficulty selecting their medications based on color which has implications for non-compliance. They are also more likely to experience frustration with their medication therapy due to color vision changes.

Aging has been the center of new research in many areas. Understanding the aging process can help society in many ways. With the growing population of older adults it is going to become even more important to understand the changes that occur with age. Senescence affects the body in many ways, taking its toll on all organ systems. The sensory organs are no exception; there have been several findings in regards to the aging and senescence of the senses, most notably vision. As with all organ systems, the visual system shows an increased risk of failure with increased age.<sup>1</sup> Most people associate vision changes only with acuity, contrast sensitivity, and visual field, which are the functions that are most associated with everyday functioning. One visual function is often overlooked, especially by healthcare practitioners, color vision and perception. Although color vision seems to many to be an insignificant change, this loss can actually cause more problems than realized before. Many understand that changes in vision are important to everyday functioning, but few understand the problems and frustrations that might occur with declines or loss of color vision. The concept of color vision is easily neglected as a practitioner, but this failure of acknowledgement can potentially lead to frustrations for older adults and ultimately misunderstandings between patient and clinician. Even with additional education in aging, it is quite easy to forget the disabilities of older adults in everyday situations. Improving healthcare for older adults presents a multitude of problems, many of these problems can be overcome with knowledge and understanding of this population.<sup>2</sup>

One of the largest problems facing healthcare and older adults is prescription non-compliance. Compliance is defined as taking the right drug, right dose, at the right time. As the population ages, there is an increased incidence of chronic disease, many older adults having one or more. With the increased morbidity of older adults there is an increased use of prescription, as well as over the counter medications. It has been found that the use of prescription medications can greatly improve quality of life and even increase one's life span. The benefits have been proven time and time again, but there still seems to be a vast problem with prescription compliance for various reasons.<sup>3</sup> Most older adults have noticeable impairment in everyday tasks, situations, and settings.<sup>4</sup> These impairments are due to a large number of problems with bodily function, but vision has been shown to be one of the key factors in maintaining independence into old age. Despite this correlation little research has been done on the association of prescription compliance to vision, let alone color vision.<sup>1</sup>

The small amount of research available established that there is a direct correlation between physical performance and several visual functions. Having a poor performance on vision function tests were correlated with self-reports and objective observations of difficulties in physical functioning.<sup>1</sup> Special note should be made that even those with relatively good vision report having difficulties with vision under everyday conditions, giving rise to concerns that general vision tests are not useful in determining vision function in older adults.<sup>4</sup> These observations are no different for prescription compliance. Vision, most importantly that for color, is used for organizational and memory cues, two functions needed for compliance. Color contrast sensitivity and discrimination ability is important in distinguishing between tablets or capsules of similar color, size, and/or shape.<sup>5</sup> Beyond this, the visual appearance of oral dosage forms is related to a patient's acceptance and compliance. If a patient does not like the appearance of a specific drug they are less likely to take it as directed.

Researchers have also found that patients associate specific colors to a drug's therapeutic function and strength. Some believe dosing medication in this manner would be beneficial allowing patients to more readily remember which medication is for which condition.<sup>6</sup> If pharmacists and physicians understand color vision changes, they will be more prepared to assist patients in developing a memory system in regards to color for their drug regimen. Without knowledge of color vision changes, attempts at assistance can cause frustration and miscommunication.

Besides color associations, color popularity can also affect the perception of a specific drug form. Researchers observed that those taking more than ten solid oral dosage form medications preferred bright colors, despite the overall popularity of white.<sup>6</sup> This observation is assumed to be related to the previous discussion on the relationship of color and memory. The more medications a person takes the more effort is needed to take them properly. Memory cues can be very useful in compliance, so it seems that those taking several medications would like each drug to be a different color as research has shown. Since a majority of older adults take multiple medications it is important to study the effects of color on the older population. While research does present significant data on color preferences, most fail to effectively take into account the changes in color vision seen in older adults.<sup>7</sup>

Given the wide variety of colors within pharmaceuticals and the high percentage of prescription sales being to older adults, one might assume developers would take into consideration the color vision changes that occur with age.<sup>8</sup> To the contrary, pharmaceutical companies appear to generalize findings on color vision perception as being associated with all age groups. Though still behind in acknowledging the many changes that come with age, the pharmaceutical industry has made strides to increase compliance. Along with these advances, healthcare practitioners must still be aware of the frustrations that color vision changes might cause. Since these changes occur gradually, it may take several years for one to notice them, if at all. With this knowledge, healthcare practitioners can more readily treat patients for a better health outcome.

Color vision expresses a variety of changes throughout one's lifetime. Overall, each aspect of color vision has been shown to decline significantly with age although at different rates and beginning at different times in one's life history. Color contrast sensitivity decreases significantly, giving rise to a lower sensitivity for color differences in older persons.<sup>9</sup> In low light, the differences between older and younger adults are greater than in high light. Essentially all ages experience the same contrast sensitivity on different spatial scales.<sup>10</sup> Colorimetric purity also decreases linearly with age, which results in the inability to distinguish between white and colors with low purity such as pastels, and can make colors of all saturations look dull.<sup>11, 12</sup> Low light adds to the challenge an older adult has in making a distinction between two similar colors; by increasing the amount of light, this difficulty decreases slightly. As established the most noticeable change in color vision is the inability to distinguish or even detect certain colors.<sup>13, 14</sup>

Changes in color vision manifest themselves in several ways, but are caused by similar mechanisms. The largest component causing color vision change is the senescence of the lens. As humans age the lens grows thicker, denser, and more spherical, reducing the radius of curvature. Changing the shape and curvature of the lens directly reduces refraction and the increased material modifies the refractive index.<sup>15</sup>

Although changes in refraction are important, they are only minor in relation to color vision. Refraction affects the amount of light reaching the retina, thus decreases in refraction cause a reduction in the amount of stimuli reaching the proper photoreceptors. Lenticular yellowing exponentially increases the absorbance of light passing through the lens. The greatest absorbance is for wavelengths between 460 and 470nm, which correspond to the blue portion of the visible spectrum. Absorbance appears to primarily affect short wavelengths with little variation in absorbance of longer wavelengths. Older persons show a higher reduction in their ability to detect those colors in the blue-violet spectrum than in the yellow-red spectrum.<sup>15, 16</sup>

In addition to changes in the lens, there are significant changes in neurotransmission. Changes in the neurons and the general structure of cones ultimately cause a decrease in the sensitivity of cone pathways. Research has shown that S-cones are more prone to damage than L or M-cones, and therefore the sensitivity of S-cones show a greater overall loss.<sup>13,17</sup> Besides decreases in cone sensitivity, several other modifications to the retina have been shown to cause declines in color vision. These would include decreased cone density, disordered arrangement of cones due to photoreceptor loss, as well as loss of nuclei in the outer nuclear layer.<sup>18</sup> The misalignment of the outer segment membrane can cause shifting in the placement of remaining cones and can therefore decrease the amount of light incident on them.<sup>19,20</sup> The sum of these changes results in major declines in color vision that are not usually recognized or addressed.

Generalizations about the entire prescription population based upon studies that that do not account for age differences in color vision can cause more problems than solutions. This study explores the difficulties that can be caused by the decreases in color vision in older adults. To the knowledge of the researchers, this is the first and only study associating color vision with medication selection. Specifically, this study used simulated age related changes in color vision as well as simulated medication to determine an association between color vision and medication selection. This study wishes to establish beyond the documented research that it is necessary to consider color vision changes when working with older adults, in addition to determining the extent to which prescription compliance might be affected by color vision changes.

## **Methods**

### **Participants**

This study used a total of 60 participants between the ages of 18 and 26. Participants were randomly selected and placed into one of two groups, control or experimental, 30 participants each. Eligibility requirements were based upon eye health. Researchers wanted to control for color blindness, glaucoma, cataracts, macular degeneration, and any other disorders of the eye that could potentially affect color vision. Volunteers with these conditions were excluded from the experiment. Due to the high prevalence of eye disorders among older adults, in addition to the increased likelihood that these disorders might go unnoticed, researchers chose to simulate age changes to avoid these confounding variables. Based on the results from a power analyses, a sample size of 60 was determined adequate to achieve at least a 95% level of confidence in difference between control and experimental group. Since the number of participants

was important, recruitment of volunteers continued until 60 eligible participants were found.

### **Procedure**

Prior to participant recruitment, the Institutional Review Board at the Ohio State University reviewed study design and the study was determined to be exempt from review by the IRB. Participants were required to read and sign a standard consent form prior to assignment to a group. A researcher explained the experiment to all participants as well as read the consent form aloud before proceeding with the participants' signature. Once consent was received, participants were randomly placed into either the control or experimental group. The only difference between the two groups was that the participants in the experimental group were asked to wear a pair of yellow-lens glasses, which are routinely used in teaching health practitioners about color vision changes in older adults (double laminated on 10 pt board with special yellow filters designed to simulate illuminance in a 70 year old person). As proven by several studies, the human lens yellows overtime and it was therefore assumed that yellow filters would simulate this. The yellow lenses used in this study are similar to those used in other studies on color vision in older adults. Suzuki, et al as well as, Okajima and Takase concluded that the simulated lenses used with younger adults were a valid proxy for studying the effects of color vision deficits in older adults.<sup>14,21,22</sup> Several studies have also used yellow filters as a way of simulating an aged lens and have found similar results.<sup>9,21-4</sup> All participants were asked several questions pertaining to their eye health prior to performing the experiment which determined their eligibility. After eligibility was determined, participants in the experimental group were asked to put on the yellow-lens glasses.

All participants were given a prescription medicine bottle containing 80 colored beads, 10 each of red, orange, yellow, green, blue, purple, white, and brown (round, 10mm wooden beads colored using ceramcoat acrylic paint). Participants were asked to select a specific number of beads according to color and place them on an ordinary paper plate. The number of beads requested according to color is shown in Table 1. In each step of the experiment, a new color was requested independently from the others, so as to evaluate each color separately and without bias. The experiment for all participants was carried out under standard desk lighting in mid-afternoon. The number correct and the colors that were mistaken were recorded. Each participant was given no time limit in which to finish the experiment. Upon completion, participants were asked several questions to further assess their thought processes throughout the experiment in addition to the overall difficulty of the experiment. Participants were asked what colors they found to be the most difficult to see and which color pairs were difficult to distinguish between. In addition, participants were asked what led them to choose a specific color bead over another, whether there was an aesthetic attribute or if the decision was made by guessing. Finally, participants were asked to rate the difficulty of the task on a scale ranging from 1=easy and 5=difficult.

## **Results**

### **Measures**

Scores were calculated as the number of beads that participants correctly selected based on the researcher's instructions to identify an individual color. Researchers were

particularly interested in several color pairs, red and orange, yellow and white, blue and green, and purple and brown. The scores from each individual color were compared between control and experimental groups as well as to its paired color in order to find relative correlations. The researcher also considered participants' responses to the researcher's questions that were asked at the end of the experiment. These responses were important in assessing differences between the control and experimental groups. The post-questions explored which colors participants felt were the most difficult to see and which color pairs were difficult to distinguish between. The total number of participants that recognized certain colors and color pairs was calculated. These totals were used in comparison with the average number of correct beads selected, particularly with the experimental group, in order to establish a relationship between how the participant felt about their decision and their actual result. The responses pertaining to the decision-making process were used to determine what other attributes of the beads were used to make a selection, which allowed the researchers to draw further conclusions on aesthetics and prescription compliance. The difficulty scores the participants gave the experiment were also compared between the two groups to find the relative difficulty between the control and the experimental group.

### **Data Analysis**

Paired t-tests were used to establish the difference between the scores of the experimental group as compared to the control group. Colors and color pairs that showed a p-value  $<0.05$  were considered to show a significant difference between the control and experimental group.

### **Results**

The number correct provided by each group was compared taking specific note of particular color pairs: red/orange, white/yellow, green/blue, and purple/brown, as well as taking into account total number of correct beads. A significant difference ( $p < 0.05$ ) between the control and experimental groups were found with all colors, with the exception of red and orange, where no significant difference was found. The control group showed no difficulty in distinguishing any of the color pairs, whereas the experimental group showed significant difficulty with all pairs with the exception of red/orange where no difficulty was shown. Percentage correct is presented in Figure 1. The most significant differences between control and experimental groups were found with purple and brown. The experimental group showed mean scores of  $.77 \pm 0.971$  (25.67%) and  $1.87 \pm 1.697$  (31.17%) respectively. Participants were more likely to make an error when selecting purple over brown with ~5% difference in percentage correct. The post-test responses further support the relative difficulty of determining the purple beads from the brown. The highest number of participants in the experimental group, 28 of 30 participants (93.3%) recognized purple/brown as one of the more challenging pairs to distinguish. In contrast, the best scores, excluding red and orange, were for yellow and white, which showed scores of  $2.40 \pm 0.855$  (80.0%) and  $5.03 \pm 1.351$  (83.83%) respectively. Participants were more able to properly select white beads over yellow beads with ~3% accuracy difference. These scores are surprising since 27 of 30 (90.0%) participants from the experimental group reported yellow and white as a difficult color pair to distinguish between. The results of the color pair blue and green closely follow

those of white and yellow, with scores of  $2.37 \pm 0.928$  (79.0%) and  $5.37 \pm 0.928$  (89.5%) respectively. The participants showed a greater ability to select green over blue, with a percentage correct difference of ~10%, showing the greatest difference between scores of any color pair. Only 24 out of 30 participants (80.0%) in the experimental group recognized blue/green as a difficult pair. Totals showed a mean score of  $24.80 \pm 3.284$  (74.44%), with high variability between subjects. Table 2 shows standard deviation, standard error mean, mean scores, and p values of t-test samples for all color pairs. One participant in the experimental group expressed difficulty in distinguishing between green and brown during the post-test. This participant also showed irregular patterns in color selection among purple, brown, blue, and green. The participant's overall score was 19 correct selections out of the possible 36 (52.78%), where the average score was 26.8 (74.44%).

Following the experiment, participants in the experimental group were asked to comment on their thought processes throughout the experiment, particularly why they chose one bead over another. The most common response was shade; most participants reported using the shade of the apparent color to decide which beads belonged together. This led many participants to select all the same color beads, but in many cases they selected beads of the incorrect color. Texture was also a frequent method in determining the correct beads to select. Several participants noticed subtle differences in the texture of the different colored beads. It is believed the texture differences were due to the paint used on the beads, which caused some beads to have a slightly different texture. Another recurrent response was pure guessing. Several participants reported guessing in order to make the proper selections, for some, this method worked, for others it did not. Additionally, all participants were asked to rate on a scale from 1 to 5 the difficulty of the task they were asked to perform, 1=easy and 5=difficult. The average difficulty score for the control group was 1.04 and the average score for the experimental group was 4.02.

**Table 1. Requested Beads**

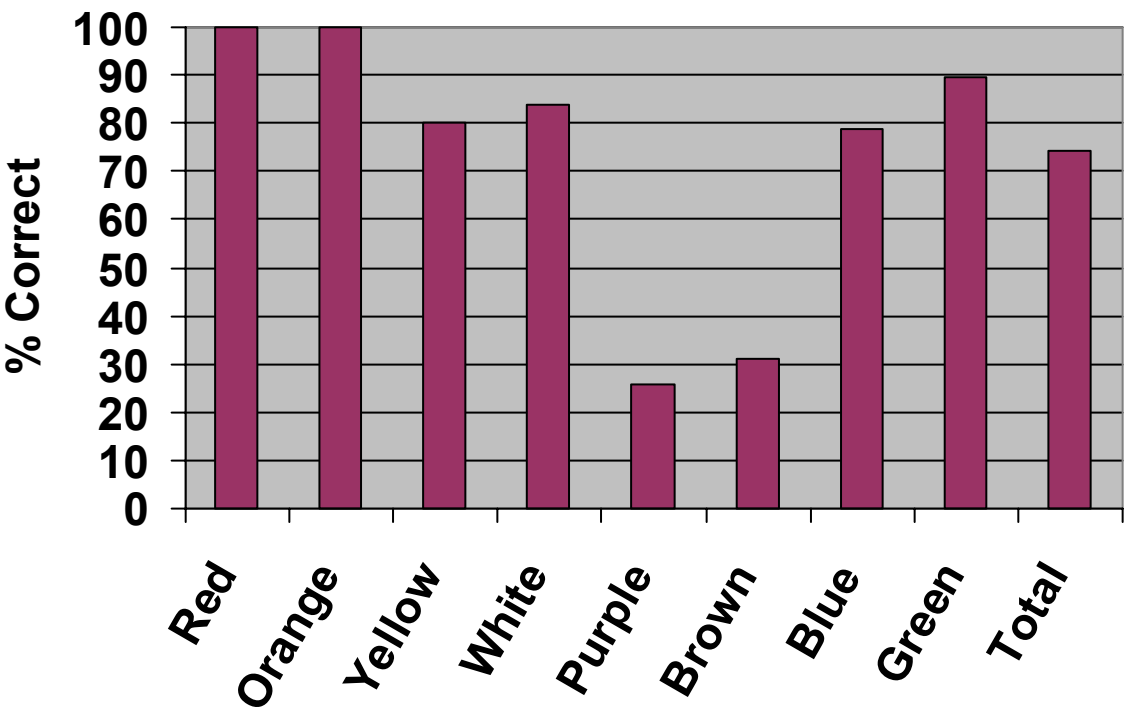
Color	# Requested
Red	3
Orange	6
Yellow	3
White	6
Purple	3
Brown	6
Blue	3
Green	6



**Table 2. Paired T-Test Samples (n = 30)**

<b>Color</b>	<b>Group</b>	<b>Mean Scores</b>	<b>Std. Deviation</b>	<b>Std. Error Mean</b>	<b>p-value</b>
Red	Experimental	3	.000	.000	No difference
	Control	3	.000	.000	
Orange	Experimental	6	.000	.000	No difference
	Control	6	.000	.000	
Yellow	Experimental	2.40	.855	.156	.001
	Control	3.00	.000	.000	
White	Experimental	5.03	1.351	.247	.000
	Control	6.00	.000	.000	
Purple	Experimental	0.77	.971	.177	.000
	Control	3.00	.000	.000	
Brown	Experimental	1.87	1.697	.310	.000
	Control	6.00	.000	.000	
Blue	Experimental	2.37	.928	.169	.001
	Control	3.00	.000	.000	
Green	Experimental	5.37	.928	.169	.001
	Control	6.00	.000	.000	
<b>Total</b>	<b>Experimental</b>	<b>26.80</b>	<b>3.284</b>	<b>.600</b>	<b>.000</b>
	<b>Control</b>	<b>36.00</b>	<b>.000</b>	<b>.000</b>	

Figure 1. Percentage Correct in Experimental Group



## **Discussion**

The geriatric population accounts for more than half of all prescriptions in the United States to date. For decades, it has been well established that color vision is impaired in the older adult population. This study has shown that impaired color vision poses significant challenges to proper medication therapy, especially as it pertains to prescription compliance. Colored beads and yellowed lens glasses were used to simulate medication selection under conditions of impaired vision. There were noteworthy differences between participants with and without the yellow lenses in their ability to select the correct colored bead. Those using the yellow lenses were not only more likely to make errors, but also showed more frustration and less confidence in their bead selection. This study has reinforced findings from previous research on color vision. As with many other studies, this study has shown that older adults have the most difficulty with colors in the blue-violet range of the color spectrum.<sup>9,11-18,20,23</sup> As a result we have found that specific pairs of colors were less likely to be differentiated than others; most notably blue and green, brown and purple, as well as white and yellow.<sup>7</sup> All participants in the experimental group reported using other visual clues to select the proper beads, including texture and shade, which for many failed to assist them in selecting the correct color. Several participants selected beads of the same color, but the incorrect color from what was requested. Some differences in percentage correct could be due to differences in number of beads requested. Participants generally scored higher when asked to select a greater number of beads, but the mean difference in error showed larger differences between the two groups when a larger number of beads were requested.

This study has established a causal relationship between color vision changes in older adults and medication selection, which has not been previously explored. Although prescription compliance is a complex issue with many variables, this study has presented another possible explanation for compliance difficulty in older adults. Other studies addressed vision changes in older adults, including visual acuity, stereopsis, and contrast sensitivity, but these studies did not address deficits in color vision. Contrast sensitivity is closely related to color vision, but cannot be considered as a basis of measurement for color vision. Since the color of prescription drugs is a key component of both marketing and counseling of these products, being able to distinguish product color is thought to be a key component of compliance.

The limitations of this study relate to study conditions and the challenge in the generalizability of the findings. All participants were healthy young adults, presumably without color vision disturbances, although their color vision was not tested for the purposes of this study. Researchers decided to exclude older adults from this study due to the higher likelihood of having eye disorders, as well as the increased possibility these disorders go unnoticed and unaddressed. The data of this study suggest only one participant deviated largely from the median, possibly as the result of undiagnosed color blindness. The experiment was conducted under optimal lighting conditions, but day to day variations available in daylight could have made a small impact on the overall lighting in the room. Threats to internal validity were minimized by randomization of subjects. Any generalization of this study's findings to older adults should be made with caution since this study used younger subjects.

The original objective of this study was to find a correlation between color-vision changes in older adults and their risk for prescription noncompliance due to physical

inability. Several studies have shown that prescription compliance is lower in older adults, which has largely been attributed to cognitive impairment. This study sought to prove that even fully cognitive patients may make medication errors due to impaired color vision. This study found that in addition to increases in the likelihood of making an error we also found an increase in frustration at the difficulty of selecting the correct colored bead. Participants wearing the lenses expressed less confidence in their selection abilities in addition to finding the task more challenging than expected and expressing frustration with their inability to make a selection even without knowing if they were correct.

There are many implications resulting from the selection of the wrong pill from a group of medications. Even given appropriate lighting, an older adult would be more likely to select the wrong drug at the wrong time of day therefore missing a dose of one drug and interrupting the dosing regimen of another. For many prescription therapies, taking the drug consistently is crucial for successful treatment. Another implication is the increased risk for overdosing if two or more medications are of similar size and shape, with color being the only discriminator. Treatment failure is common in older adults and has largely been attributed to non-compliance.<sup>25-29</sup> This study has shown that there is a strong likelihood for selecting the wrong medication due to color deficiencies in the older population.

Many drugs are color coded by strength, most commonly warfarin. All generics of this product must match the color of brand Coumadin®. This system was devised to ensure patient safety in both dispensing and in managing a complicated drug regimen. There have been many concerns as to whether or not this was a useful tool in preventing medication errors. In 2005, the FDA held a hearing regarding color labeling in which presenters expressed concern that there was little efficacy seen in using color coding and in fact may be harmful to patients. Several presenters argued that perhaps this might make drug regimens more difficult for older adults due to their color vision deficiencies.<sup>30</sup> This study has shown color vision deficiencies can make a seemingly simple task very challenging. Furthermore, beyond color requirements of warfarin, there are many generic brands for the same drug and no regulations require them to be the same color as the brand drug. So for a given drug there can be multiple formulations all differing in color therefore minimizing the likelihood that from refill to refill customers will get the same color product. If the drug color is continually changing, using color to distinguish between drugs is not entirely feasible.

On average, adults over the age of 60 use millions of prescription drugs each year, making their drug regimens more complicated. Color is a seemingly easy way for healthcare providers to assist their patients with complex dosing regimens. Although this has become a common practice, healthcare providers need to be more aware of the potential complications that can occur as a result. Miscommunications can arise if a patient is told their medication is going to be purple, but to them it appears brown. Patient's might feel additional frustration, confusion, and question whether they are receiving the correct medication. A potential solution would be to show patients the medications they will be taking as the pharmacist counsels them, without referring to color. This would allow patients to make their own memory cues based on color, shape, and texture of the medication. Not only would miscommunication and confusion be minimized, but the patient would be more comfortable and confident in their medication

therapy. To better prepare future healthcare professionals, educators should incorporate curricular elements that expose students to the challenges faced by the older populations. During therapeutics courses and in practice counseling sessions, it would be beneficial to use age sensitivity exercises to help students apply therapeutic topics to the older population.

Healthcare practitioners are not the only group that would benefit from applying knowledge of color vision deficits in the older population. The pharmaceutical industry continually employs psychology to decide the color of their drug and many companies sponsor their own research into color preferences. Most of these studies do not include many, if any, patients over the age of 65.<sup>6-8</sup> Without inclusion of this population these results cannot be generalized to this population. Those studies that have been directed toward the geriatric population have found similar results to this study, but are few in number.<sup>8</sup> Considering these findings, drug companies still advertise with colors that are difficult for older adults to see. In order to best serve older adults, all of their physical difficulties should be considered, including color vision.

To best apply the results of this study, pharmaceutical companies should consider the inclusion of older adults in studies on perception and acceptance of oral dosage forms. Furthermore, it is difficult to fully generalize the results of this study to older adults since it only simulated age-related changes, therefore more studies like this should be done comparing actual older adults with younger adults. Future research should also be considered to more fully explain the functional implications of color vision loss. Continued research should be done to analyze the best ways in which to counsel older patients on their drug regimen based upon the results found in this study.

## **References**

1. West CG, Gildengorin G, Haegerstrom-Portnoy G, Schneck ME, Lott L, Brabyn JA. Is vision function related to physical functional ability in older adults?. JAGS. 2002 Jan;50(1):136-145.
2. Noyes MA. Pharmacotherapy for Elderly Women. J Am Med Womens Assoc. 1997 Summer;52(3):138-141,158.
3. Murray MD, Morrow DG, Weiner M, Clark DO, Tu W, Deer MM, Brater DC, Weinberger M. A conceptual framework to study medication adherence in older adults. Am J Geriatr Pharmacother. 2004 Mar;2(1):36-43.
4. Brabyn J, Schneck M, Haegerstrom-Portnoy G, Lott. The Smith-Kettlewell Institute (SKI) longitudinal study of vision function and its impact among the elderly: an overview. Optometry and Vision Science. 2001 May;78(5):264-9.
5. Windham BG, Griswold ME, Fried LP, Rubin GS, Xue QL, Carlson MC. Impaired vision and the ability to take medications. JAGS. 2005 Jul;53(7):1179-1190.
6. Lüscher M. The psychological influence of capsule colours on the therapeutic effect of a drug. News sheet, Capsugel Library 1992, B-2880 Bornem, Belgium.
7. Overgaard ABA, Hojsted J, Hansen R, Moller-Sonnergaard J, Christrup LL. Patient's evaluation of shape, size and colour of solid dosage forms. Pharm World Sci, 2001;23(5):185-188.
8. Hersberger J and Hatebur S. Differentiation between and preference for colours and colour combinations of hard gelatin capsules by the elderly. News sheet, Capsugel Library 1997, B-2880 Bornem, Belgium.
9. Fiorentini A, Porciatti V, Morrone MC, Burr DC. Visual ageing: unspecific decline of the responses to luminance and colour. Vision Res. 1996;36(21):3557-3566.
10. Delahunt PB & Hardy JL. Senescence of spatial chromatic contrast sensitivity. II. matching under natural viewing conditions. J Opt Soc Am A. 2005 Jan;22(1):60-67.
11. Kraft JM & Werner JS. Aging and the saturation of colors. 1. colorimetric purity discrimination. J Opt Soc Am A, 1999 Feb;16(2):223-230.
12. Kraft JM & Werner JS. Aging and the saturation of colors. 2. scaling of color appearance. J Opt Soc Am A, 1999 Feb;16(2):231-235.
13. Nguyen-Tri D, Overbury O, Faubert J. The role of lenticular senescence in age-related color vision changes. IOVS. 2003 Aug;44(8):3698-3704.
14. Suzuki T, Qiang Y, Sakuragawa S, Tamura H, Okajima K. Age-related changes of reaction time and the p300 for low-contrast color stimuli: effects of yellowing of the aging human lens. J Physiol Anthropol. 2006;25:179-187.
15. Pierscioneck BK & Weale RA. The optics of the eye-lens and lenticular senescence. Documenta Ophthalmologica. 1995;89:321-335.
16. Weale RA. Age and the transmittance of the human crystalline lens. Journal of Physiology. 1988;395:577-587.
17. Gao H & Hollyfield JG. Aging of the human retina: differential loss of neurons and retinal pigment epithelial cells. IOVS. 1992 Jan;33(1):1-17.
18. Shinomori K, Scheffrin BE, Werner JS. Age-related changes in wavelength discrimination. J Opt Soc Am A. 2001 Feb;18(2):310-318.
19. Keunen JEE, van Norren D, van Meel GJ. Density of foveal cone pigments at older age. IOVS. 1987 Jun;28(6):985-991.

20. Scheffrin BE, Shinomori K, Werner JS. Contributions of neural pathways to age-related losses in chromatic discrimination. *J Opt Soc Am A*. 1995 Jun;12(6):1233-1241.
21. Okajima K and Takase M. Effect of wearing spectacles to simulate the aging of the human lens in the color naming of Muncell Color Chips. *J Illum Engng Inst Jpn*. 2000;84(11):839-42.
22. Okajima K and Takase M. Computerized simulation and chromatic adaptation experiments based on a model of aged human lens. *Optical Review*. 2001 Jan;8(1):64-70.
23. Ishihara K, Ishihara S, Nagamachi M, Hiramatsu S, Osaki H. Age-related decline in color perception and difficulties with daily activities-measurement, questionnaire, optical and computer-graphics simulation studies. *Int J Ind Ergon*. 2001 Sept-Oct;28(3-4):153-163.
24. Yoshida CA and Sakuraba S. The use of films to simulate age-related declines in yellow vision. *J Occup Rehabil*. 1996 Jun;6(2):119-134.
25. Dutta S and Reed RC. Effect of delayed and/or missed enteric-coated divalproex doses on valproic acid concentrations: simulation and dose replacement recommendations for the clinician. *J Clin Pharm Ther*. 2006;31:321-9.
26. Hermida RC, Ayala DE, Khder Y, Calvo C. Ambulatory blood pressure-lowering effects of valsartan and enalapril after a missed dose in previously untreated patients with hypertension: a prospective, randomized, open-label, blinded end-point trial. *Clin Ther*. 2008;30(1):108-120.
27. Hernandez RH, Armas-Hernandez MJ, Chourio JAC, Armas-Padilla MC, Lopez L, Alvarez M, Pacheco B. Comparative effects of amlodipine and nifedipine GITS during treatment and after missing two doses. *Clin Pharmacol*. 2001;6(1):47-57.
28. Lacourcière Y and Asmar R. A comparison of the efficacy and duration of action of candesartan cilexetil and losartan as assessed by clinic and ambulatory blood pressure after a missed dose, in truly hypertensive patients. *AJH*. 1999;12:1181-7.
29. Tan KW and Leenen FHH. Persistence of anti-hypertensive effect after missed dose of perindopril. *J Clin Pharmacol*. 1999;48:628-630.
30. FDA: U.S. Food and Drug Administration [Internet]. Bethesda (MD): Center for Drug Evaluation and Research; c2008. [Transcript], Public Hearing: Use of Color on Pharmaceutical Product Labels, Labeling and Packaging; [updated 2005 Oct 14; cited 2008 April 21]; [about 13 pages]. Available from: [http://www.fda.gov/cder/meeting/part15\\_3\\_2005/Transcript.pdf](http://www.fda.gov/cder/meeting/part15_3_2005/Transcript.pdf)